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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,481	02/10/2004	Scott A. Waldman	100051.11601 WAL_SCO.008	1053
35148	7590	10/18/2010	EXAMINER	
Pepper Hamilton LLP 400 Berwyn Park 899 Cassatt Road Berwyn, PA 19312-1183			REDDIG, PETER J	
			ART UNIT	PAPER NUMBER
			1642	
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			10/18/2010	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/775,481	<b>Applicant(s)</b> WALDMAN ET AL.	
	<b>Examiner</b> PETER J. REDDIG	<b>Art Unit</b> 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08/03/2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 64,65,68-70,72,74,75,91-103,132,145,147,148 and 150-174 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 64,65,68-70,72,74,75,91-103,132,145,147,148 and 150-174 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>08/27/2010</u> .  | 6) <input type="checkbox"/> Other: _____                          |

Art Unit: 1642

### **DETAILED ACTION**

1. The Amendment filed August 3, 2010 in response to the Office Action of February 3, 2010 is acknowledged and has been entered. Claims 169 and 170 have been amended. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are currently under consideration as drawn to the previously elected species of 5-fluorouracil and bleomycin.

#### ***New Grounds of Rejection***

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

Art Unit: 1642

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,879,656 (March, 1999, previously cited), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8, previously cited), in further view of US Pat. No. 6,251,439 (Baron Jun. 26, 2001, previously cited), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033, previously cited), and in further view of Riechmann et al (Nature Vol 332:323-327 1988, previously cited).

US Patent No. 5,879,656 teaches administering anti-guanylyl cyclase C antibodies, including monoclonal and chimeric, and GCC ligands in conjugated and unconjugated form with therapeutic agents to individuals for therapy of primary or metastasized colorectal cancer, see claims 30-31, col. 10-lines 33-45, col. 25-26, and col. 45-lines 1-10. US Patent No. 5,879,656 teaches that individuals suffering from primary and metastasized colorectal cancer can be readily identified and the compositions of the invention can be used to kill the cancer cells, see col. 7-lines 30-65. US Patent No. 5,879,656 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 5,879,656 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 17-lines 25-33. US Patent No. 5,879,656

Art Unit: 1642

teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 17 and 18. US Patent No. 5,879,656 teaches multiple therapeutic agents such as 5-fluorouracil and bleomycin, see the claims and col. 21-lines 35-65.

US Patent No. 5,879,656 teaches as set forth above, but does not teach the different doses, concentrations, and times of treatment claimed, humanized anti-guanylyl cyclase C monoclonal antibody or treating with calcium.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

US Pat. No. 6,251,439 (Baron Jun. 26, 2001) teaches a method for reducing the risk of colorectal adenoma using calcium, see claims and Example.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of USPN 5,879,656 and use different doses and times of infusion of the unconjugated GCC ligands, such as uroguanylin, and antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would

Art Unit: 1642

have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

It would have been *prima facie* obvious and one of skill in the art would have been motivated to additionally administer calcium in combination with the methods of US Patent No. 5,879,656 for treating colorectal cancer because US Pat. No. 6,251,439 teaches that calcium treatment reduces the risk of colorectal adenoma development and one of skill in the art would be motivated reduce the risk of further cancer development to prevent further suffering of the patient using the combined methods. One of skill in the art would have a reasonable expectation of success as calcium has been successfully used for the prevention of colorectal adenomas.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Queen et al teach a reproducible technique for making humanized monoclonal antibodies (page 11030, col. 2 para 3) and further teaches that for human applications humanized monoclonal antibodies are more useful because of their reduced immunogenicity (page 10029, col. 2).

Art Unit: 1642

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat (monoclonal) antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to and one of ordinary skill in the art would have been motivated to make and use humanized monoclonal forms of the anti-GCC antibodies of 5,879,656 with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized monoclonal antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse monoclonal antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Art Unit: 1642

Applicants argue that they have amended claims 169 and 170 to recite that the ligand or the antibody is unconjugated. The combination of references cited by the Office fails to yield the presently claimed invention. The Office has failed to show that the claims are *prima facie* obvious in view of the cited references. Accordingly, the claims are not obvious.

Applicants' arguments have been considered, but have not been found persuasive because USPN 5,879,656 teaches using unconjugated GCC ligand compositions for treatment as set forth above. See col. 25 and 26. Additionally, applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

3. Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147-148 and 150-174 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,767,704 (Waldman March 27, 2000, previously cited), in view of Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157, previously cited), in further view of US Pat. No. 6,251,439 (Baron Jun. 26, 2001, previously cited), and in further view of Cohen (Int J Radiat. Oncol. Biol. Phys, 1987, 13:251-8, previously cited).

US Patent No. 6,767,704 teaches administering conjugated and unconjugated GCC ligands and anti-guanlyl cyclase C humanized monoclonal antibodies with therapeutics to individuals for therapy of primary or metastasized colorectal, stomach or esophageal cancer, see claims col. 3-lines 50-55, col. 21-lines 55-60, col. 22-line 55 to col. 23-line 67, col. 29, 30 and col. 31-lines 63-67. US Patent No. 6,767,704 teaches that the compositions of the invention can

Art Unit: 1642

be used to kill the cancer cells, see col. 21-lines 45-55. US Patent No. 6,767,704 teaches that the pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. US Patent No. 6,767,704 teaches that the treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously. See col. 26-lines 4-11. US Patent No. 5,879,656 teaches using intravenous infusion of the compositions and that the dosage is varied depending several factors including pharmacodynamics, route of administration, and kind of concurrent treatment. See col. 26.. US Patent No. 6,767,704 teaches multiple therapeutic agents such as 5-fluorouracil and bleomycin, see col. 22-line 55 to col. 23-line 67. Thus, given that US Patent No. 6,767,704 teaches administration of the antibodies and conventional chemotherapies, such as the described therapeutic agents, in combination sequentially or simultaneously, one of skill in the art would immediately envision administering the antibody and different therapeutic agents in the claimed order.

US Patent No. 6,767,704 teaches as set forth above, but does not teach the different doses, concentrations, and times of treatment claimed, or treating with calcium.

Shilubhai et al. teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1.

US Pat. No. 6,251,439 (Baron Jun. 26, 2001) teaches a method for reducing the risk of colorectal adenoma using calcium, see claims and Example.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the

Art Unit: 1642

tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time. See abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of USPN 6,767,704 use different doses and times of infusion of the unconjugated GCC ligands, such as uroguanylin, and antibodies comprising therapeutic agents, because Shilubhai teaches the anti-cancer activity of uroguanylin and Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

It would have been *prima facie* obvious one of skill in the art would have been motivated to additionally administer calcium in combination with the methods of US Patent No. 6,767,704 for treating colorectal cancer because US Pat. No. 6,251,439 teaches that calcium treatment reduces the risk of colorectal adenoma development and one of skill in the art would be motivated reduce the risk of further cancer development to prevent further suffering of the patient using the combined methods. One of skill in the art would have a reasonable expectation of success as calcium has been successfully used for the prevention of colorectal adenomas.

It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results. Additionally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art

Art Unit: 1642

unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05(II).

Applicants argue that they have amended claims 169 and 170 to recite that the ligand or the antibody is unconjugated. The combination of references cited by the Office fails to yield the presently claimed invention. The Office has failed to show that the claims are *prima facie* obvious in view of the cited references. Accordingly, the claims are not obvious.

Applicants' arguments have been considered, but have not been found persuasive because USPN 6,767,704 teaches using unconjugated compositions as set forth for treatment as set forth above. See col. 29 and 30. Additionally, applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

4. All other objections and rejections recited in February 3, 2010 are withdrawn.
5. No claims allowed.
6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1642

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/  
Primary Examiner, Art Unit 1642